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Effects of Chronic Oral Monosodium Glutamate Consumption on Naloxane-Induced Morphine Withdrawal in Infant Rats

Kronik Monosodyum Glutamat Tüketiminin Yavru Sıçanlarda Naloksonla Tetiklenen Morfin Yoksunluğu Üzerine Etkileri

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ABSTRACT

Aim: The aim of this study was to investigate chronic oral monosodium glutamate (MSG) consumption effects on symptoms of withdrawal, locomotor activity, and anxiety in morphine withdrawal syndrome induced by naloxone in infant rats.

Material and Methods: Twelve 21-day-old male Wistar rats used in the study. Infant rats were given unlimited access to saline (control group) or MSG (MSG group) added to drinking water for 32 days. Withdrawal was induced by naloxone in morphine-dependent rats. Evaluation of withdrawal symptoms and anxiety were performed simultaneously with locomotor activity measurements. Unpaired two-tailed t-test was used for statistical analysis.

Results: Withdrawal sings, such as jumping, wet dog shake, and weight loss; stereotypic, ambulatory, and vertical locomotor activity movements; central, peripheral, and total activities used in the assessment of anxiety in infant rats with naloxone-induced withdrawal syndrome that consumed oral MSG for 32 days were not different from the control group.

Conclusion: These findings obtained in our study indicate that chronic consumption of oral MSG in infant rats whose blood-brain barrier has not yet developed does not affect morphine dependence and naloxone-induced withdrawal. Further studies are needed to investigate the mechanism of action of orally administered MSG.

Keywords: Anxiety, Jumping, Locomotor activity, Weight loss, Wet dog shake

ÖZ

Amaç: Bu çalışmanın amacı yavru sıçanlarda ağızdan kronik monosodium glutamate (MSG) tüketiminin naloksonla tetiklenmiş morfin yoksunluk sendromunda yoksunluk bulguları, lokomotor aktivite ve kaygı üzerine etkilerinin araştırılmaktır.

Gereç ve Yöntemler: Çalışmada on iki adet 21 günlük erkek Wistar sıçan kullanılmıştır. Yavru sıçanların içme suyuna ilave edilen salin (kontrol grubu) veya MSG'e (MSG grubu) 32 gün boyunca

sınırsız erişimleri sağlandı. Morfin bağımlılığı geliştirilen hayvanlarda yoksunluk nalokson ile tetiklendi. Yoksunluk bulgularının ve kaygının değerlendirmesi lokomotor aktivite ölçümleri ile eşzamanlı yapıldı. İstatistiksel analizde unpaired two-tailed t-testi kullanıldı.

Bulgular: 32 gün boyunca ağızdan MSG tüketen sıçanlarda naloksonla tetiklenen yoksunluk sendromunda zıplama, ıslak köpek silkinmesi ve kilo kaybı gibi yoksunluk bulguları; stereotipik, ambulatuvar ve vertikal lokomotor aktivite hareketleri ve kaygının değerlendirilmesinde kullanılan santral, periferik ve total aktiviteler kontrol grubundan farklı değildi.

Sonuç: Çalışmamızda elde edilen bu bulgular MSG'ın kan-beyin bariyeri henüz gelişmeyen yavru sıçanlarda kronik oral tüketiminin morfin bağımlılığını ve naloksonla tetiklenen yoksunluğunu etkilemediğine işaret etmektedir. Ağızdan alınan MSG'ın etki mekanizmasının araştırması için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Kaygı, Zıplama, Lokomotor aktivite, Kilo kaybı, Islak köpek silkinmesi

INTRODUCTION

Morphine is an opioid analgesic that is commonly used to management severe pain (1). However, repeated exposure to morphine leads to tolerance, dependency, and withdrawal syndrome that limit its use (2). The mesocorticolimbic dopaminergic system, which project from the ventral tegmental area to the nucleus accumbens and medial prefrontal cortex plays an important role in the dependence and withdrawal of morphine and other opioids (3). It is thought that there is a complex mechanism in the pathogenesis of opioid dependence and withdrawal, including dopamine as well as neurotransmitters or neuromodulators such as glutamate, gamma aminobutyric acid, noradrenaline, serotonin, vasopressin, substance P, neuropeptide Y, and nitric oxide (2-6).

Monosodium glutamate (MSG), used to flavor foods, is the sodium salt of glutamate, the main excitatory neurotransmitter of the central nervous system (CNS), which is found in high concentrations in the brain areas such as the cerebral cortex, cerebellum, and hippocampus (7). According to previous studies, the effects of MSG differ according to the route of administration (7). While MSG is associated with increased satiety, appetite regulation, decreased sodium consumption without affecting taste, metabolic disorders and convulsions when administered orally, it causes hypothalamic damage, short stature, metabolic disorder and weight gain when administered parenterally (7). Oral MSG creates the taste of umami by stimulating taste buds on the tongue taste-mGluR4 and T1R family receptors, stimulates the vagus nerve, probably via increased production of bioactive substances by activating the specific receptors in the gastrointestinal tract and mediates indirect effects in the CNS (7,8). Due to the modulatory role of the glutamatergic system in addiction and withdrawal mechanisms, the effects of MSG, an exogenous glutamate, on dependence and withdrawal have been investigated in few studies before (9-11). Oral MSG has previously been demonstrated to be effective in initiating oral ethanol consumption in rats (9). Both orally and parenterally administered MSG has been shown to elicit signs of endogenous opioid dependency in rats, as well as withdrawal syndrome induced by the opioid antagonist naloxone in rats (10,11).

The aim of this study was to investigate chronic (32-days) oral MSG consumption effects on symptoms of withdrawal, locomotor activity, and anxiety in morphine withdrawal syndrome induced by naloxone in infant rats.

MATERIAL and METHODS

Animals

In this study, a total of twelve male infant Wistar rats (21-day-old, weight of 75-95g) were used in two groups as control (n = 6) and MSG (n = 6). All experimental procedures in accordance with the 'Guide for the Care and Use of Laboratory Animals' were approved by the Local Ethics Committee for Animal Experiments of Marmara University (MUHDEK 12/12/2018-109.2018.mar). The study was carried out between February and April 2019 with rats obtained from Experimental Animals Application and Research Center of Marmara University (DEHAMER). These rats with unlimited access to standard rat chow were housed with a reversed 12 hours light/dark cycle at 21±3°C and 50±5% humidity.

Experimental Procedure

1.0 g/L NaCl and 1.0 g/L MSG (Sigma-1446600) were added to the drinking water of the control and MSG groups, respectively. In order to prevent possible low consumption and mask the bad taste, 24 g/L sucrose was added to the water of both groups and rats were provided unlimited access to this water for 32 days (7). Three slow-release morphine pellets containing morphine base were placed to rats subcutaneously (s.c.) under mild ether anesthesia on days 28 (one pellet) and 30 (two pellets) of oral MSG or NaCl consumption. On day 32 of oral MSG or NaCl consumption, withdrawal was induced in morphine-dependent rats with 3 mg/kg intraperitoneal (i.p.) naloxone hydrochloride dihydrate (Sigma-N7758) which was dissolved in saline and were placed immediately to the center of the 40 × 40 × 40-cm open area test apparatus (Locomotor Activity Cage, AMS 9701, Commat Ltd.,) for 15 minutes (12). In the open-field activity (central, peripheral, and total activities) which

was used on anxiety evaluation, and LMA (stereotypic, vertical and ambulatory movements) measurements, the integrated Activity Metering Software II version 2.1 was used, in which the location of the experimental animal was recorded every 100 milliseconds via infrared photocells. Morphine withdrawal syndrome signs such as wet dog shake (WDS) and jumping were assessed simultaneously with LMA and open-field activity measures (4,5,13). To determine body weight loss, each rat was weighed just before withdrawal was triggered and immediately after simultaneous open-field activity and LMA measurements and assessment of withdrawal syndrome signs (4,5). The rats were sacrificed under high-dose sodium thiopental anesthesia at the end of the experiment.

Statistical Analysis

Data analysis was done with GraphPad Prism 5.01 software. Kolmogorov-Smirnov test was performed to test whether the parametric test assumptions were met. Groups were compared with an unpaired two-tailed t-test, with results presented as mean ± standard error of mean (SEM). $p<0.05$ was considered significant in all statistical calculations.

RESULTS

There was no statistically significant difference in findings such as jumping (1.7±0.62, $p>0.05$), WDS (8.4±1.44, $p>0.05$) and weight loss (12.25±1.03, $p>0.05$) in naloxone-induced withdrawal syndrome of morphine-dependent infant rats that consumed oral MSG for 32 days compared to the saline-consuming control group (1.83±0.7, 12.5±2, 14±0.97, respectively) (Figure 1).

There was no statistically significant difference in stereotypic ($p>0.05$), ambulatory ($p>0.05$) and vertical ($p>0.05$) LMA movements in naloxone-induced morphine withdrawal between the MSG (320.3±41.62, 705±38.9, 22.44±1.69, respectively) and the control groups (361.1±32.11, 741.9±53.9, 24.8±3.37, respectively) (Figure 2).

There was no statistically significant change in the central ($p>0.05$), peripheral ($p>0.05$) and total activities ($p>0.05$) used in the evaluation of anxiety in the MSG group (9.73±2.89, 8.75±2.28, 1415±96.68, respectively) compared to the control group (14.75±2.63, 5.49±1.48, 1433±107.8, respectively) in morphine withdrawal induced by naloxone (Figure 3).

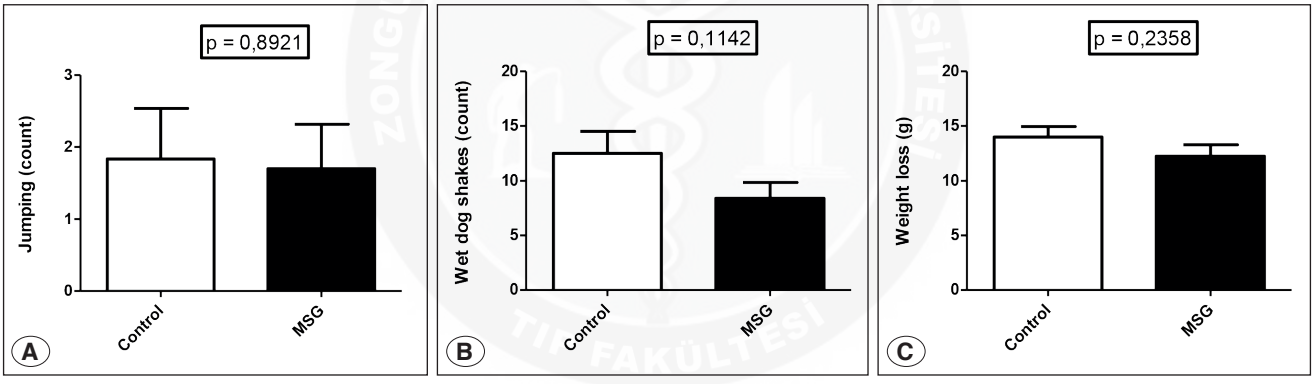

Figure 1: The effects of orally consumed monosodium glutamate (1.0 g/L, n = 6) for 32-days on jumping **(A)**, wet dog shakes **(B)**, and weight loss **(C)** in naloxone-induced withdrawal syndrome in morphine-dependent infant rats. The control group consumed 32-day per-orally NaCl (1.0 g/L, n = 6). Results were expressed with mean ± standard error of mean.

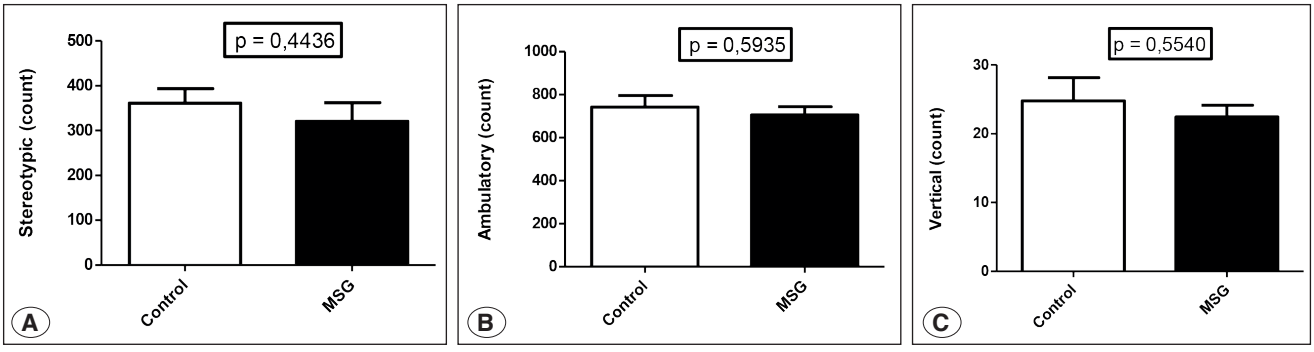

Figure 2: The effects of orally consumed monosodium glutamate (1.0 g/L, n = 6) for 32-days on stereotypical **(A)**, ambulatory **(B)**, and vertical **(C)** LMA movements in withdrawal syndrome induced via naloxone in infant rats. The control group consumed 32-day per-orally NaCl (1.0 g/L, n = 6). Results were expressed with mean ± standard error of mean.

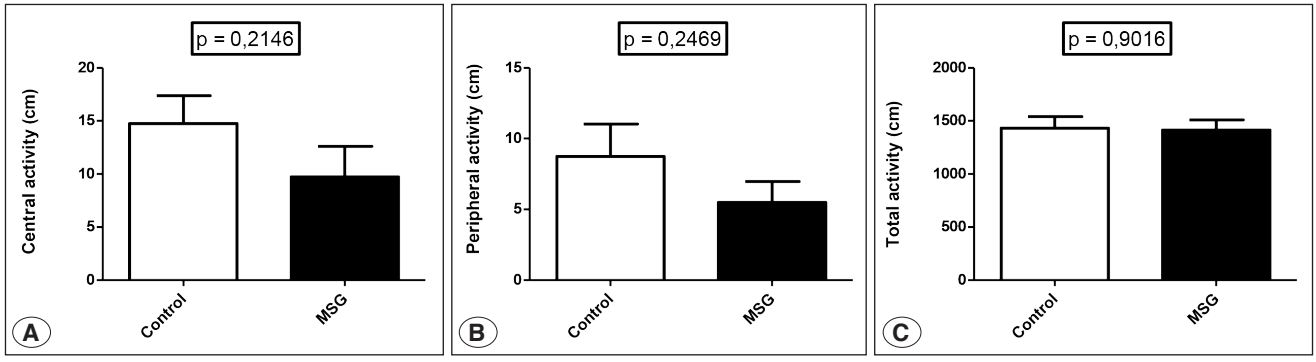

Figure 3: The effects of orally consumed monosodium glutamate (1.0 g/L, n = 6) for 32-days on central **(A)**, peripheral **(B)**, and total **(C)** activities in naloxone-induced withdrawal syndrome in infant rats. The control group consumed 32-day per-orally NaCl (1.0 g/L, n = 6). Results were expressed by mean ± standard error of mean.

DISCUSSION

The findings of this study are that there was no significant difference in withdrawal signs such as jumping, WDS and weight loss, in stereotypic, ambulatory and vertical LMA movements, in the central, peripheral and total activities (used in the evaluation of anxiety) in naloxone-induced withdrawal syndrome of morphine-dependent infant rats consuming 32-days oral MSG compared to the saline-consuming control group.

The studies examining the effects of MSG on dependence and withdrawal are limited (9-11,14,15). Oral MSG has previously been shown to induce conditioned place and flavor preference in adult rodents (14,15). In addition, oral MSG was found to be successful in initiating oral ethanol consumption in mice (9). It has been reported that adult rats consuming 12 hours/day MSG orally for 8 days show signs of endogenous opioid addiction and withdrawal syndrome is induced after a 12-hour deprivation time or naloxone application (10). In the same study, an increase in the withdrawal index calculated as sum of the head shaking, teeth chattering, tremors of forepaw, and WDS was observed in MSG withdrawal syndrome (10). These effects were thought to be due to pleasant and positive emotional sensations associated with the sodium in the MSG consumed orally, as well as subchronic exposure (10). Physical dependence may not occur, as constant consumption of pleasant-tasting substances causes changes in taste receptors and suppression of positive reinforcing effects due to chronic exposure (16). However, MSG does not only exert its effect by stimulating taste receptors, it may also affect brain regions that modulate the reward center, since it creates an indirect effect on brain regions via vagal nerve fibers by stimulating its receptors in the gastrointestinal tract (7,8,17). In another study, withdrawal symptoms such as WDS and jumping were evaluated in naloxone-induced withdrawal syndrome in rats administered s.c. MSG postnatally and developed morphine dependence at 3 and 14 months (11). It was observed that WDS was exacerbated in 3 months and suppressed in 14 months, on the contrary, jumping was suppressed in 3 months and exacerbated in 14 months (11). According to the authors, this is due to the destruction of brain regions responsible for addiction by neonatally parenterally MSG treatment and the development of relatively less severe age-related opiate physical dependence (11). According to previous studies, parenterally administered MSG affects the plasma glutamate level at a level that can exceed the blood-brain barrier (BBB) and increases the brain glutamate levels (18). It is thought that oral MSG is metabolized in the gastrointestinal tract, only 5% of it passes into the portal circulation and increases plasma glutamate levels, but this increase is not at a level that can exceed the BBB (18,19). It is known that the increase in central glutamate levels are associated with brain damage, neurochemical changes, neurodegeneration, loss of interest and decreased sensitivity to reward (20,21). Therefore, glutamate levels are maintained with high sensitivity by excitatory amino acid transporters (EAAT) and excess glutamate is removed from the environment by converting to glutamine for reuse (20,21). Unlike these studies, we used 21-day-old infant rats with a just weaned and had an immature BBB, given unlimited and chronic (32-days) access to orally MSG, and observed that naloxone-induced morphine withdrawal signs were not different from saline-consuming control group. This may be due to the fact that chronic exposure to oral MSG in infant rats with an immature BBB and lacked the enzymes required to metabolize MSG, does not affect central glutamate levels to a level that causes destruction in brain regions responsible for addiction, even if it crosses the BBB (22). This may also be due to the balance of the increased brain glutamate levels caused by oral MSG, with EAAT in a short time, in infant rats (22).

Jumping and WDS behaviors in rodents in morphine withdrawal syndrome have been associated with dopaminergic and serotonergic systems, respectively (23,24). The glutamatergic system also plays an important role in morphine

withdrawal syndrome (3). Indeed, previous studies have shown that riluzole, which inhibits glutamate release, glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor antagonists suppresses morphine withdrawal signs, while kainic acid, a glutamate analog, causes behaviors similar to morphine withdrawal (25-28). Based on this information, in our study, exogenous glutamate consumed orally for 32-days was expected to lead to an increase in withdrawal signs such as jumping and WDS in the naloxone-induced withdrawal syndrome. However, in our study, these withdrawal findings were found to be indistinguishable from the control group. As stated above, this may be because exogenous glutamate does not affect the levels of central glutamate to stimulate glutamatergic receptors in the brain regions responsible for dependence, even if it crosses the BBB, and/or the increased brain glutamate levels re stabilized in a short time through EAAT.

Morphine causes constipation by decreasing gastrointestinal secretions, suppressing gastrointestinal motility, increasing water absorption from chyme and anal sphincter tone (2). Although morphine-induced constipation occurs predominantly as a result of the peripheral effect, the contribution of the central effect should not be ignored (29). Naloxone reverses morphine-induced constipation, causing diarrhea and weight loss (30). The finding of weight loss in morphine withdrawal syndrome induced by naloxone in infant rats chronically exposed to oral MSG were also not significantly different from the control group in our study. This finding may be due to the fact that chronic oral MSG did not affect central glutamate levels much, even if it crossed the BBB, and/or did not have a central effect as a result of high-sensitivity protection of glutamate levels by EAAT, as in the jumping and WDS findings.

In addition to withdrawal signs, an increase in LMA movements is observed in morphine withdrawal syndrome (31). This may have emerged as a result of modulation in both c-fos levels and the dopaminergic system due to repeated use of opioids (32,33). The effects of MSG on the LMA have been studied before and the results have been found to be inconsistent. In rats neonatally treated with s.c. MSG, initial LMA was increased, while at 2 months of age it was decreased (34). Adult rodents i.p. applied MSG caused a decrease in LMA (35,36). On the other hand, oral MSG both decreased and increased LMA in adult mice (36-39). In our study, stereotypical, ambulatory and vertical LMA movements of infant rats receiving chronic MSG orally were not different from the saline-consuming control group. This may be due to the fact that chronic oral MSG did not increase the central glutamate levels much, even if it crossed the BBB, and/or increased glutamate levels was quickly balanced by EAAT, as in the withdrawal findings.

The final finding of our study is that in withdrawal syndrome induced by naloxone in morphine-dependent infant rats consumed orally MSG for 32-days, the central, peripheral, and total activities were not significantly different compared to the saline-consuming control group. These parameters are used in the evaluation of anxiety in rodents, spending less time in the central area or low central activity, spending more time in the peripheral area or having more peripheral activity indicates that there is anxiety (40). Studies investigating the effects of subchronic and chronic exposure to oral MSG on anxiety in both infant and adult mice using the elevated plus maze demonstrated anxiolytic-like behavior in some and anxiety-like behavior in others (39,41-43). In the forced swimming tests, in which the effects of oral MSG on anxiety were investigated, the results were found to be contradictory, it was seen that it both increased and suppressed anxiety (37,44). In a study examining the effects of oral intermittent MSG on total motor activity, it did not differ from controls (10). The finding of the last research was found to be compatible with our study. The fact that the anxiety finding observed as a result of chronic exposure to oral MSG in the infant rats we preferred in our study was not significantly different from the saline-consuming control group, is probably because, as with the withdrawal symptoms and LMA, it did not increase the central glutamate levels much, even though exogeneous glutamate has crossed the BBB. These findings may also be due to the brain glutamate levels being maintained precisely by EAAT.

It was determined that chronic oral MSG consumption, known as the most commonly used natural form of glutamic acid, the main excitatory neurotransmitter of the CNS, did not affect withdrawal signs, LMA and anxiety in naloxone-induced morphine withdrawal in rats whose BBB was not yet mature. This could be because oral MSG does not have a destructive effect on the infant brain and/or is rapidly removed from brain tissue and preventing its harmful effects, rather than because it does not cross the BBB. Further studies, such as measuring glutamate levels in brain regions, are needed to investigate the central mechanism of action of orally administered MSG.

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Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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Ethical Approval

All experimental procedures in accordance with the 'Guide for the Care and Use of Laboratory Animals' were approved by the Local Ethics Committee for Animal Experiments of Marmara University (MUHDEK 12/12/2018-109.2018.mar).

Review Process

Extremely peer-reviewed and accepted.

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